Environmental Health Perspectives Supplements
101 (Suppl. 2): 125–130 (1993)

Environmental Release of Chemicals and Reproductive Ecology

by J. S. Bajaj,[1] A. Misra,[1] M. Rajalakshmi,[1] and R. Madan[2]

Reproductive ecology is defined as "the study of causes and mechanisms of the effects of environmental risk factors on reproductive health and the methods of their prevention and management." Major areas of concern, within the purview of this paper, relate to adverse pregnancy outcomes, effects on target tissues in the male and the female, and alterations in the control and regulatory mechanisms of reproductive processes. Teratogenic potential of chemicals, released as a result of accidents and catastrophes, is of critical significance. Congenital Minamata disease is due to transplacental fetal toxicity caused by accidental ingestion of methyl mercury. Generalized disorders of ectodermal tissue following prenatal exposure to polychlorinated biphenyls have been reported in Taiwan and Japan. The Bhopal gas disaster, a catastrophic industrial accident, was due to a leak of toxic gas, methyl isocyanate (MIC), in the pesticide manufacturing process. The outcome of pregnancy was studied in female survivors of MIC exposure. The spontaneous abortion rate was nearly four times more common in the affected areas as compared to the control area (24.2% versus 5.6%; $p < 0.0001$). Furthermore, while stillbirth rate was found to be similar in the affected and control areas, the perinatal and neonatal mortality rates were observed to be higher in the affected area. The rate of congenital malformations in the affected and control areas did not show any significant difference. Chromosomal aberrations and sister chromatid exchange (SCE) frequencies were investigated in human survivors of exposure. The observed SCE frequencies in control and exposed groups indicated that mutagenesis has been induced. Strategies for the management, prediction, and preventability of such disasters are outlined.

Introduction

Never before in the history of mankind has there been such a vast multiplicity of environmental risk factors, nor has there been such expression of concern regarding inherent danger of their likely impact on diverse aspects of human health, including reproductive health. The term "reproductive ecology" is defined as "the study of causes and mechanisms of the effects of environmental risk factors on reproductive health and the methods of their prevention and management."

Health is defined in the constitution of the World Health Organization (WHO) as "a state of complete physical, mental and social well being, and not merely the absence of disease or infirmity." In the context of this positive perspective, reproductive health has been defined as "a state in which the reproductive process is accomplished in a state of complete physical, mental and social well being, and is not merely the absence of disease or disorders of the reproductive system" (*1*). The indexes of reproductive health, therefore, need to be defined both in terms of the ability to reproduce and also with regard to the successful outcome of the reproductive process which includes infant and child survival and growth and healthy development. Furthermore, the definition of the reproductive health has been further elaborated and amplified so as to imply that people have the ability to reproduce, to regulate their fertility, and to practice and enjoy sexual relationships. Reproductive health also implies that reproduction leads to a successful outcome through infant and child survival, growth, and healthy development. Finally, the term implies that women can go safely through pregnancy and childbirth, that fertility regulation can be achieved without health hazards, and that people are safe in having sex" (*2*). The ascertainment of impact of environmental release of chemicals on reproductive health, therefore, must be within the scope of these considerations and must relate to the proposed definition of reproductive ecology. Major areas of concern, within the purview of this paper, relate to adverse pregnancy outcomes, effects on target tissues in the male and the female, and alterations in the control and regulatory mechanisms of the reproductive processes.

The teratogenic potential of chemicals, released as a result of accidents and catastrophes, is of critical signifi-

[1]SRB Centre of Clinical Pharmacology, Department of Medicine, All India Institute of Medical Sciences, New Delhi, India 110029.

[2]Department of Obstetrics and Gynaecology, SMGS Medical College, Jammu, Jammu and Kashmir, India.

This manuscript was presented at the Conference on the Impact of the Environment on Reproductive Health that was held 30 September–4 October 1991 in Copenhagen, Denmark.

cance. Although originally defined as abnormal morphogenesis, the conceptual framework of teratogenesis has now been broadened to include all adverse outcomes, including death of the conceptus, malformations, deformations, growth retardation, and developmental disabilities. Furthermore, "developmental" includes not only physical but also cognitive and behavioral attributes.

It may be worth reiterating that environmental exposures to chemicals, whether at the workplace or through accidental release, and irrespective of the route of entry (e.g., ingestion, inhalation, or dermal contact) follow the sequential pathways of pharmacokinetics regarding absorption, transport, metabolic biotransformation, tissue distribution, storage, and excretion. As a sound knowledge of clinical pharmacokinetics provides the basis of clinical therapeutics, similarly, an understanding of pharmacokinetics of any environmental chemical is vital to the assessment of risk following human exposure. The final health outcomes relate to the pharmacodynamics of the specific compound or compounds in the case of multiple exposures.

It is appropriate to briefly describe some of the well-characterized disorders due to accidental release of chemicals and their effects on reproductive health. The intention is not to review in detail the total clinical symptomatology of each syndrome, but to use these examples as model case studies so as to build a possible strategy for evaluation, risk assessment, remedial intervention, and prevention.

Minamata Disease

Congential Minamata disease is due to intrauterine methyl mercury poisoning. In 1955, many cases of a severe neurological disorder were found in the Minamata area of Kyushu, Japan. It was only 3–4 years later that a link was definitely established between the toxic release of methyl mercury from an acetaldehyde plant of the Chisso Corporation as an effluent into the Minamata Bay, where it was ingested by fish which were subsequently eaten by pregnant women, thus producing fetal toxicity (*3,4*). This was the first good example of combining sound epidemiological methods and critical clinical observation to establish clinicopathological correlation, to produce an experimental model, and finally to confirm a transplacental route of fetal toxicity. It may be recalled that during pregnancy no abnormalities were observed in mothers of affected children, nor was any conspicuous abnormality demonstrated in the newborn. It was only at the beginning of the 6th month after birth that symptoms were recognized.

Although not well appreciated at that time, a subsequent literature search showed that the disease had been reported by Engelson and Herner in Sweden in 1952 (*5*) in people eating seed grain treated with alkyl mercury. This highlights the need for establishing a sound database through international cooperation to facilitate early data retrieval and recognition of symptoms. Similar cases have been subsequently reported in diverse geographical locations (*6–8*).

Minamata disease manifests at around 6 months of age. The prominent manifestations include: severe delay in developmental parameters mainly due to muscular incoordination, persistence of primitive reflexes, and mental symptoms (*9*) (Table 1). The affected subjects generally have hypotonia, nystagmus, pendular knee jerk, ataxia, speech disturbances, and extrapyramidal movement disorders. Most of these clinical symptoms and signs are due to cerebellar dysfunction. In addition, there may be spasticity of limbs, hyperactive reflexes, and strabismus. This constellation of symptoms and signs is indicative of pyramidal involvement. Finally, these symptoms may occur singly or in combination. A condition resembling akinetic mutism may also be observed in the affected children. It may be difficult to distinguish these children from those affected by cerebral palsy. However, it may be noted that strabismus, cerebral symptoms, and disturbances of higher mental functions are more marked in congenital Minamata disease. Follow-up studies over the last 15 years have shown that cerebellar symptoms and persistence of primitive reflexes may improve over a period of time. However, no improvement has been observed in intellectual functions.

Table 1. Clinical features of congenital Minamata disease.[a]

Symptoms	Frequency, %
Impaired intelligence	100
Primitive reflex	100
Cerebellar dysfunction	100
Growth retardation	100
Limb deformities	100
Hyperkinesis	95
Strabismus	77
Pyramidal disorder	75

[a]Adapted from Harada (*9*).

The detailed pathological studies have revealed pyramidal tract dysmyelination, hypoplastic corpus callosum, and degeneration of the granular cell layer of the cerebellum (*10*). It is the last feature that is most characteristic and explains prominent symptoms and signs of cerebellar dysfunction. Sophisticated experimental studies have proved that administration of methyl mercury to pregnant cats leads to organic brain dysfunction (*11,12*). Using the technique of autoradiography, transplacental passage of mercury has been confirmed (*13*). Epidemiological studies (*6,14*) have shown high methyl mercury concentrations in the umbilical cord blood of the affected children.

Agent Orange and PCBs

During the Vietnam war, a toxic chemical, "Agent Orange," was sprayed widely over the crops for the purpose of defoliation, covering almost 10% of the Vietnamese countryside. This chemical consists of equal proportions of *n*-butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) contaminated by small amounts of highly toxic dioxin. Agent Orange has been observed to be teratogenic in mice and other animals (*15*). Some of the studies (*16–18*) have provided suggestive evidence of the teratogenic effects of Agent Orange in humans, though available data are not compelling. In a case–control study (*19*), it was observed that Vietnam war veterans were not at a higher overall risk for fathering babies with birth defects, though the

risk of individual abnormalities like spina bifida and cleft palate was higher.

Polychlorinated biphenyls (PCBs) have been extensively used for commercial purposes in electrical appliances, hydraulic oils, and as additives for a variety of painting materials. Contamination of the environment has occurred due to improper disposal of these chemicals. Studies in the Federal Republic of Germany (*20*) indicated that PCB is present in human fat and milk. A further analysis of a large number of samples showed that mean level of PCB/kg fat can be as high as 8.3 mg (*21*).

Rogan et al. reported two detailed studies on PCB exposure in Japan and Taiwan (*22,23*). In 1979, poisoning from cooking oil contaminated by thermally degraded PCB occurred in Taiwan. *In utero* exposure of this chemical occurred in children born to affected women because this contaminant persisted in the human tissues. The predominant toxic manifestations were on skin and other ectodermal tissues. These babies had a typical skin discoloration and were called "cola-colored babies." There may be abnormalities of other organ systems such as the lungs. The exposed children were shorter and weighed less than the controls. Other noteworthy features were delay of developmental milestones, deficits in development, and abnormalities of behavior. The ingestion of contaminated cooking oil is reminiscent of the discovery of gossypol and its antifertility effects following the ingestion of cottonseed oil (*24*).

Methyl Isocyanate

The Bhopal gas disaster, recognized as one of the worst industrial catastrophes, has raised several pertinent issues that are the subjects of intensive completed or ongoing studies, supported by the Indian Council of Medical Research. Although the quantity of data generated so far is large, only the published findings shall be reviewed.

Bhopal, the capital city of the State of Madhya Pradesh in Central India, was the site of an industrial accident during the night of December 2–3, 1984. The cause was the leak of a toxic gas, methyl isocyanate (MIC), used in the pesticide manufacturing process. MIC is a small molecule that reacts rapidly with sulfydryl, carboxyl, and hydroxyl groups, thus producing widespread tissue damage. Following MIC exposure, two major studies were initiated. The first study was aimed at ascertaining pregnancy outcomes in those who had been exposed to MIC during gestation (*25*). This study was carried out in 10 severely affected areas of Bhopal city around the Union Carbide factory. A door-to-door survey was conducted in April–May 1985 (about 6 months after the disaster) to identify all women who were pregnant at the time of exposure, as determined by recording those who had their last menstrual period before November 18, 1984. For purposes of recruiting controls, an unaffected area was later included, with the inclusion of subjects with their last menstrual period before November 18, 1985. In all, there were 18,978 households in the affected area, with approximately 86,000 subjects. In the control area, there were 13,539 households with approximately 60,000 subjects (Table 2).

Table 2. Pregnancy outcome following the Bhopal gas disaster.[a]

Parameter	Affected area	Control area
Population covered (no. of subjects)	18,978	13,539
Total number of pregnancies	2,566	1,218
Number of women at risk of abortion	1,468	485
Number of spontaneous abortions	355	27
Abortion rate, %	24.2*	5.6*
Number of induced abortions	26	3
Intermediate fetal death (21–27 weeks of gestation)	32	8

[a]Adapted from Bhandari et al. (*24*).
*$p < 0.001$.

Abortion has been defined as termination of pregnancy before 20 weeks of gestation. Therefore, only those women who were up to 20 weeks of gestation on March 12, 1984 were considered to be at risk of abortion. There were 1468 such women at risk in the affected area and 485 in the control area. The number of spontaneous abortions was four times higher in the affected area (Table 2).

Detailed analyses were undertaken with respect to age, period of gestation, socioeconomic status, religion, and consanguinity. Although the mean age of the women included in the study in the affected area (24.9 years) was similar to that of the control area (24.4 years), there was a significant difference in the number of women who were 30 years of age or older (21.6% in the affected versus 15.7% in the control areas, $p < 0.01$). A further analysis, therefore, of the age-specific data in the affected area showed that the abortion rate was significantly higher (32.5%) in the women over 30 years old as compared to those in less than 30 years old (22.1%). There was no case of abortion in women 30 years old or older in the control area. Comparative analysis following age standardization showed an abortion rate of 23.6% in the affected and 5.6% in the control area. Most of the women were from the low socioeconomic strata. The proportion of Muslims and of consanguinity was considerably higher in the affected area. There was no significant correlation of abortion rate with religion or consanguinity. Women with a period of gestation less than 20 weeks on December 3, 1984, were at considerably higher risk in the affected area as compared to the control area. The risk of intermediate fetal death (21–27 weeks) was 1.2% in the affected area and 0.7% in the control area (Table 2).

Stillbirths, defined as pregnancies terminated at 28 weeks of gestation or later, were similar in affected and control areas (Table 3). Data on early neonatal mortality indicates that 95 babies died within 7 days of birth in the affected area compared to 33 babies in the control area. Similarly, there were 129 deaths in the neonatal period (up to 28 days of birth) in the affected areas as compared to 52 deaths in the control. The comparison of the above data indicates significantly higher perinatal and neonatal mortality in the affected area (Table 3). The rate of congenital malformations was 14.2/1000 births in the affected area compared to 12.6/1000 births in the control area and hence was not significantly different (Table 3). No cytogenetic studies were done on the aborted fetuses; thus genetic

Table 3. Pregnancy outcome following the Bhopal gas disaster.[a]

Parameter	Affected area	Control area
No of deliveries	2153	1180
No. of live births	2117	1160
No of still births	56	27
Still birth rate/1000 deliveries	26.0	22.9
No. of early neonatal deaths (0–7 days)	95	33
Total perinatal loss	151	60
PMR/1000 births	69.48*	50.54*
No. of neonatal deaths (0–28 days)	129	52
NMR/1000 live births	60.9†	14.8†
No. of congenital malformations	31	15
Rate/1000 births	14.2	12.6

Abbreviations: PMR, perinatal mortality rate; NMR, neonatal mortality rate.

[a]Adapted from Bhandari et al. (*24*).

*$p < 0.001$.

†$p < 0.001$.

damage as a possible underlying mechanism could not be confirmed.

The second study was aimed at formulating a chromosomal profile of asymptomatic and symptomatic human survivors following MIC exposure (*26*). This longitudinal study explored possible genetic effects as a result of MIC exposure (*26*). Chromosomal aberrations and SCE frequencies were investigated. SCE analysis is generally considered to be a sensitive method for detection of mutagenic effects because it represents reciprocal interchange of DNA between chromatids at apparently homologous loci. There was a considerably higher frequency of SCE in the MIC-exposed individuals, indicating induction of mutagenicity in the subjects Furthermore, chromosomal breaks, gaps, and small chromatin bodies were observed to occur at a higher frequency in MIC-exposed subjects, thus providing further evidence of chromosomal damage. In a later publication (*27*), it was recorded that among apparently normal subjects exposed to MIC, 20% possess various chromosomal abnormalities. Pathological complications (e.g., tumors, etc.) may develop in some of these subjects. Among the chromosomal abnormalities, Robertsonian translocations, mostly in acrocentric chromosomes 13 and 21, have been frequently recorded. Other types of translocations involving chromosomes 5, 9, 11, 14, and 16 were also observed to be significantly higher in the MIC-exposed subjects. The significance of these findings in relation to reproductive health is not entirely clear.

Management and Prevention

Individual patient management following exposure to a specific chemical is based on the consideration of *a*) the nature of the chemical, *b*) its pharmacokinetics including half-life, *c*) likely concentrations in those tissues with a high affinity for that chemical agent, *d*) the possible human exposure dose, *e*) the route of entry, *f*) absorption, *g*) transportation within the body, *h*) metabolic degradation, and *i*) route(s) of excretion. However, in this paper a general framework for the development of policy guidelines is presented for the purpose of discussion and possible adoption.

Ascertainment and Reporting

Identifying the nature of the chemical, and initiating urgent action for immediate data retrieval regarding its pharmacokinetics and specific antidote, if any, is important. Reports must take into consideration of any national, state, or local law which may make it mandatory or obligatory to report exposures to predefined chemical agents. In several countries, environmental agencies or health departments have proscribed sets of rules and regulations in this respect. In some countries, reporting is immediately followed by advice from the agency regarding specific methods of management that may be adopted. In some cases, specific antidotes may be quickly transported to the area where the accidental environmental exposure to a chemical has taken place. Finally, an investigative procedure may be launched to delineate the causes underlying such accidental exposure and to suggest remedial measures to prevent a recurrence in the future. However, the practices vary from state to state and from country to country. In many parts of the developing world, no such mechanisms exist. There is therefore a need to facilitate the development of a basic sequential framework that could be applied globally. It is suggested that an International Disaster Early Alert and Action System (IDEAS) be established. To emphasize the proposed acronym, it is an idea whose time has come.

Surveillance

It is helpful to differentiate between the concepts underlying medical surveillance and disease surveillance. The former is a clinical strategy and aims at evaluation of individuals at periodic intervals for the purposes of identifying any clinical or laboratory alterations suggestive of exposure. On the other hand, disease surveillance is essentially a public health strategy that aims at observing large populations or subsets of populations for any demonstrable indicators of changing incidence of specific diseases or groups of disorders. In the context of accidental exposure to environmental chemicals, and, more specifically, reproductive ecology, both these concepts are applicable. Although follow-up of individuals directly exposed to environmental chemicals who survive the immediate effects is essential over a period of time as part of medical surveillance, observation of the whole population exposed to such a risk but with differential dose effects over time may provide useful information regarding reproductive health, including adverse pregnancy outcomes. Guidelines need to be established for important industrial chemicals for the clinical and laboratory parameters to be included as core components of the surveillance program.

Quality Control

As the detection, management, and surveillance of environmental exposures depends on valid laboratory data, the quality control of the laboratory test procedures is an essential prerequisite.

Development of Infrastructure and Its Linkages with a National Health Care System

As a strategy for the prediction and prevention of adverse effects on reproductive health due to environmental chemicals, there is a need to strengthen infrastructural facilities and to develop such facilities in countries where these may not yet be available. Some of the critical elements of such an infrastructure may include the organizations below.

Reproductive Ecology Registry

The nonavailability of adequate information in many parts of the world continues to be the single most important impediment to the prediction, prevention, and management of the adverse effects of environmental chemicals on human health. In contrast, in several parts of the developed world where the requisite information does exist, its utilization through the estab shment of special links with health care systems still has to be developed. It is, therefore, essential to define a global strategy responsive to national and regional needs and directed to health and eco-surveillance programs. Essential to such a strategy would be the establishment of national registers to develop databases responding to one or more components of the defined global strategy. Interlinkages with the existing national health information systems would be essential.

The proposed registry that may be prepared, maintained and continually updated at the HRP (Human Reproduction Programme) of WHO will aim at maintaining the reproductive health profile(s) in relation to effects of environmental risk factors on reproductive health. Such a registry will serve as an international resource, both for the dissemination of information to member states and for data retrieval in response to the needs of any member country. The registry should establish links with other available databases within the framework of environmental health hazards, aiming at the development of a networking mechanism with other international organizations and designated agencies in other member countries, where similar information systems may exist or are under development.

Environmental Protection Agencies

In the United States and in some countries of Europe environmental protection agencies exist. They play a major role in proposing legislative measures and actions to protect humans from the undesirable and unhealthy effects of environmental pollution. While this broad objective is shared by most of these agencies, the specific objectives may differ. What is required is a broad, functional framework wherein the concept of the environment is multidimensional and includes biological, physical, chemical, nutritional, sociological, and demographic components. An international set of guidelines needs to be prepared in relation to the conceptual framework, structural organization, and mechanism of operation of such agencies to develop an international network of such organizations.

WHO and Other International Organizations

An unmet need of developing countries is the lack of trained manpower in several fields related to reproductive ecology. These include area-specific epidemiology, laboratory methods, developmental and reproductive toxicology, and in cooperation with organization of health information systems. WHO and other international agencies can play a major role in the development of appropriate manpower for developing countries by ascribing the designation of "WHO Collaborating Centre for Reproductive Ecology" to recognized institutions in developed countries. A specific responsibility for the education and training of scientists and technologists from developing countries could be assigned to such centers. Prioritizing research needs and providing financial support to multicentric studies are other important areas for action.

Curricular Reforms in Education and Training

Faculties of medicine, public health and law must review the curricular content of their graduate and postgraduate education programs to ensure appropriate instruction and training related to environmental hazard from chemicals. The educational objectives of such curricular reforms must be clearly stated, and strategies of problem-based learning adopted to ensure an active interest of the trainees in the educational programs. The broad objective of all such courses should be to enable qualified professionals to respond with sensitivity to human needs in the context of prevention of environmental disease and promotion of environmental health.

Professional Associations

Awareness regarding the possible risks of environmental pollution and knowledge about their prevention must receive the attention of organized groups, such as medical and scientific professional associations (physicians, surgeons, forensic experts, obstetricians and gynecologists, geneticists, toxicologists, pharmacologists, etc.), as well as nonmedical associations (industrial organizations, manufacturers, organized labor groups, etc.). Area-specific action plans need to be developed and supported. Such action plans may be developed by each group with time-targeted programs to enable evaluation of achievement of objectives over a specified period of time.

Nongovernmental Organizations

Nongovernmental organizations (NGOs) have an important role to play at the national, regional, and international levels, as they serve as bridges between national governments, international organizations, and the public. The

NGOs must have access to information with respect to environmental risk factors and their likely impact on reproductive health. They should also have adequate representation on the policy-planning bodies. Special representation needs to be accorded to the groups advocating the cause of vulnerable and disadvantaged groups such as minorities, women and children, and those who are otherwise socially disadvantaged. Generating community awareness and initiating organized community action should be important tasks of the NGOs.

Epilogue

It is abundantly clear that the concerns regarding environmental pollution due to release of chemicals are genuine and widespread. Several international disasters in recent years have shown the degree of inadequacy both in mounting immediate relief and in organizing long-term responses for health care and research. Research efforts need to be intensified in several areas of reproductive health that may be affected by environmental risk factors. International organizations must play a significant role in the transfer of appropriate technology from the developed to the developing countries, ensuring that trained manpower in adequate numbers is available in the developing world to derive immediate and maximal benefits from these technologies.

REFERENCES

1. Fathalla, M. F. Promotion of research in human reproduction: global needs and perspectives. Hum. Reprod. 3: 7–10 (1988).
2. Fathalla, M. F., Rosenfield, A., Indriso, C., Sen, D. K., and Ratnam, S. S., Eds. *Reproductive Health – Global Issues 67. Parthenon Publishing* Group, Park Ridge, NJ, 1990.
3. Kitamura, S., Hirano, Y., Noguchi, Y., Kojima, T., Kakita, T., and Kuwaki, H. The epidemiological survey on Minamata disease (No. 2). J. Kumamota Med. Soc. 33(suppl. 3): 569–571(1950).
4. Kitamura, S., Kakita, T., Kojoo, J., and Kojima, T. A supplement to the results of the epidemiological survey on Minamata disease (No. 3). J. Kumamoto Med. Soc. 34(suppl. 3): 476–480 (1960).
5. Engleson, G., and Herner, T. Alkyl mercury poisoning. Acta Paediatr. 41: 289–294 (1952).
6. Harada, M. Intrauterine poisoning, clinical and epidemiological studies and significance of the problem. Bull. Inst. Const. Med. (suppl.)25: 1–60 (1976).
7. Synder, R. D. Congenital mercury poisoning. N. Engl. J. Med. 284: 1014–1016 (1971).
8. Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. Intra-uterine methylmercury poisoning in Iraq. Pediatrics 54: 587–595 (1974).
9. Harada, M. Congenital Minamata disease: intrauterine methylmercury poisoning. Teratogen Update 18: 258–288 (1978).
10. Matsumoto, H., and Takeuchi, T. Fetal Minamata disease, a neurological study of two cases of intrauterine intoxication by a methylmercury compound. J. Neuropathol. Exp. Neurol. 24: 563–574 (1965).
11. Morikawa, N. Pathological studies on organic mercury poisoning. I. Experimental organic mercury poisoning in cats and its relation to the causative agent of Minamata disease. II. Experimental production of congenital cerebellar atrophy by bimethylmercuric sulfide in cats. Kumamoto Med. J. 14: 506–532 (1961).
12. Moriyama, H. A study on the congenital Minamata disease. J. Kumamoto Med. Soc. 41: 506–532 (1967).
13. Fujita, F. Experimental studies of organic mercury poisoning, on the behaviors of Minamata disease causal agent in the maternal bodies and its transference to, their infants via either placenta or breast milk. J. Kumamoto Med. Soc. 43: 37–62 (1969).
14. Harada, M. Study on methylmercury concentration in the umbilical cords of the inhabitants born in the Minamata area. Brain Dev. 9: 79–84 (1977).
15. Friedman, J. M. Does Agent Orange cause birth defects? Teratology 29: 193–221 (1984).
16. EPA. Preliminary Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2, 4, 5-T Spray Practices. Washington, DC, 1979.
17. Field, B., and Kerr, C. Herbicide use and incidence of neural-tube defects. Lancet i: 1341–1342 (1979).
18. Hanify, J. A., Metcalf, P., Nobbs, C. L., and Worsley, K. J. Aerial spraying of 2,4,5-T and human birth malformations: an epidemiological investigation. Science 212: 349–351 (1981).
19. Erickson, J. D., Mulinare, J., McClain, P. W., Fitch, T. G., James, L. M., McClearn, A. B., and Adams, M. J., Jr. Vietnam veterans' risks for fathering babies with birth defects. J. Am. Med. Assoc. 252: 903–912 (1984).
20. Acker, L., and Schulte, E. Uber das Vorkommen chlorierter Kohlenwasserstoffe im menschlichen Fettgewebe und in Humanmilch. Dtsch. Lebensm.-Rdsch. 66: 385–390 (1970).
21. Acker, L., and Schulte, E. Chlorkohlenwasserstoffe im menschlichen Fett. Naturwissenschaften 61: 32 (1974).
22. Rogan, W. J. PCBs and cola colored babies: Japan 1968, and Taiwan 1979. Teratogen Update 26: 259–261(1982).
23. Rogan, W. J., Gladen, B. C., Hung, K. L., Koong, S. L., Shih, L. Y., Taylor, J. S., Wu, Y. C., Yang, D., Rogan, N. B., and Hsu, C. C. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 241: 334–336 (1988).
24. Prasad, M. R. N., and Diczfalusy, E. New contraceptives for men. What are the prospects? Int. J. Androl. 6: 305–309 (1983).
25. Bhandari, N. R., Syal, A. K., Kambo, I., Nair, A., Beohar, V., Sexena, N. C., Dabke, A. T., Agarwal, S. S., and Saxena, B. N. Pregnancy outcome in women exposed to toxic gas at Bhopal. Ind. J. Med. Res. 92: 28–33 (1990).
26. Goswami, H. K. Cytogenetic effects of methyl isocyanate exposure in Bhopal. Hum. Genet. 74: 81–84 (1986).
27. Goswami, H. K. Search for chromosomal variations among gas-exposed in Bhopal. Hum. Genet. 84: 172–176 (1990).